UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

ANDREW BOURNE, a minor by and through his Parents, next friends and natural guardians, Chris Bourne and Maggie Bourne,

Plaintiff

v. Civil Action No. 2:97-0090

E.I. DUPONT DE NEMOURS AND COMPANY, INC.,

Defendant

MEMORANDUM ORDER[1]

This matter is before the court on the motion of defendant E.I. DuPont De Nemours and Company, Inc. ("DuPont") to exclude the testimony of Dr. Charles Vyvyan Howard and Dr. Randall L. Tackett, plaintiff's causation experts in the above-styled toxic tort action, filed December 5, 2001. Inasmuch as plaintiff's principal expert, Dr. Howard, has been extensively deposed on multiple occasions and Dr. Tackett has also been

[1] Following the issuance of the court's memorandum order of January 11, 2002, counsel for the plaintiff requested that the evidentiary deposition of Dr. David M. Ozonoff taken December 17, 2001, be made a part of the record in this case, to which the defendant had no objection. The court has seen fit to withdraw its memorandum order of January 11, 2002, in order that the section on epidemiology there set forth on pages 20 through 24 may take into account Dr. Ozonoff's testimony at his evidentiary deposition.

deposed and inasmuch further as the motion has been the subject of extensive submissions by both parties, the court concludes and the parties agree that the record is complete and a hearing on the motion is not needed.

I.

Minor plaintiff Andrew Bourne ("Bourne") by and through his parents, Christopher Bourne ("Mr. Bourne") and Maggie Bourne ("Mrs. Bourne"), all residents of Essex, England, filed this action in February of 1997 against DuPont alleging that Mrs. Bourne's exposure to the DuPont-manufactured agricultural fungicide Benlate, while pregnant with the plaintiff, caused plaintiff to be born with severe birth defects.[2]

Mrs. Bourne contends that she purchased Benlate from a local nursery to use in her home garden in March of 1986. (Mrs. Bourne Dep. at 39-41.) The Benlate was packaged in small sachets

---

[2] During the pendency of this case, as will be more fully noted, the parties have engaged in studies of Benlate's active ingredient, benomyl, and any relationship it may have to plaintiff's anophthalmia (the complete absence of eyes). The defendant completed and made available a pharmacokinetic study in early 1999. To rebut that study, the plaintiff was then allowed the time required to undertake a human dermal absorption study ("TNO study") that was completed in June, 2000. Plaintiff was permitted still further time to pursue a follow-up to that study that was completed in March, 2001.

roughly the size of an individual-serving sugar packet, with each sachet containing 2.25 grams of Benlate powder, approximately 53% of which was comprised of Benlate's active ingredient, the chemical benomyl. (Upstone Aff. at 5.) Also supplied with the Benlate were separate sachets containing 3.0 grams of a surfactant called "Activex." (Id.) According to the directions contained in the package of Benlate, each sachet of Benlate powder was to be mixed with a sachet of Activex along with one UK gallon of water, approximately 4.5 liters, before application on plants. (See copy of Benlate label, attached as Ex. C to Upstone Aff.)

Mrs. Bourne contends that she followed the instructions and mixed a sachet of the Benlate and a sachet of the Activex in a gallon of water. Mrs. Bourne says that she sprayed the entire gallon of the Benlate-Activex-water mixture (hereinafter "Benlate mixture") on her home garden every ten to twelve days from March through late June, 1986. (Mrs. Bourne Dep. 39, 45-47, 68.) She testified at deposition that she applied the Benlate mixture liberally to her beans, strawberries, and roses, using a watering can, and when the beans grew taller, using both a watering can and a hand sprayer. (Id. at 38-40, 43-46, 91.) She testified

that it took her approximately 45 minutes to one hour to mix and apply the Benlate mixture to her plants. (Id. at 105.)

Mrs. Bourne wore no gloves or protective face covering while working with the Benlate. (Id. at 98-100.) She testified that some Benlate powder got on her hands when she prepared the Benlate mixture and that the Benlate mixture got on her hands and perhaps her legs as she mixed. (Id. at 84-85.) When applying the Benlate mixture to her plants, she testified that the solution would get on her hands, legs, feet, and possibly face. (Id. at 85, 92-94, 96-97, 109.) She would bathe every day or every other day. (Id. at 128.)

Mrs. Bourne became pregnant with the plaintiff on or about May 5, 1986. (Ravits Dep. at 5-6.) The child was born on January 27, 1987, with bilateral clinical anophthalmia (the complete absence of eyes), hypogonadatropic hypogonadism (a pituitary disorder resulting in this case in small stature and underdeveloped genitalia), and mental retardation. (Mrs. Bourne Dep. at 128.) It is plaintiff's contention that his mother's repeated exposure to Benlate during critical periods in his fetal development led to his birth defects. (Pl.'s Compl. at ¶ 39.)

II.

In a toxic tort case, a plaintiff must generally establish both general and specific causation for his injuries. Bourne must establish that he, via his pregnant mother, was exposed to a human teratogen, both at a level and by a means capable of causing his birth defects. He must also establish that the exposure to the teratogen did, in fact, bring about his particular maladies. Drs. Howard and Tackett both opine that Mrs. Bourne was exposed to Benlate, which they contend to be a human teratogen, at a critical stage in her son's fetal development, with the Benlate being absorbed into her blood stream at a level capable of causing Bourne's defects. They rule out genetic causes for Bourne's birth defects, and each opines that Mrs. Bourne's Benlate exposure is more likely than not the cause of her son's anophthalmia. In their reports, neither Dr. Howard nor Dr. Tackett refers to the cause of the plaintiff's birth defects other than the anophthalmia.

Dr. Howard is the senior lecturer at the University of Liverpool in the Faculty of Medicine. He is a licensed medical practitioner and a fetal toxio-pathologist. According to his report, in reaching his conclusions, Dr. Howard relied upon various studies and reports involving Benlate, the deposition

transcripts of the Bournes, reports of plaintiff's expert witnesses and plaintiff's physicians, the existing epidemiology studies[3] on Benlate, the United States Environmental Protection Agency ("EPA") and the European Community's classification of benomyl, his personal knowledge and experience, and "information previously identified in [his] deposition in this case and those taken in Castillo." (Id. at 1.)

Dr. Tackett is a pharmacologist and a professor of pharmacology and Toxicology at the University of Georgia. Dr. Tackett reached the same conclusion as Dr. Howard with respect to the causation of Bourne's anophthalmia. His opinion is based upon "(1) the known pharmacological/toxicological actions of Benlate which have been demonstrated to produce anophthalmia; (2) exposure to Benlate at a critical time in Mrs. Bourne's pregnancy; and (3) the fact that dermal absorption of Benlate results in systematic levels of benomyl and its metabolites in humans." (Tackett report at 1.)

---

[3] Epidemiological studies examine the pattern of disease in human populations.

A. Mrs. Bourne's exposure to Benlate

Dr. Howard estimated the amount of Benlate to which Mrs. Bourne was dermally exposed, and Dr. Tackett adopted the estimate. Based upon Mrs. Bourne's deposition transcript, Dr. Howard opined that 30% of Mrs. Bourne's skin was exposed to 5% of the gallon of Benlate mixture each time she applied the Benlate to her plants every 10 to 12 days. The 5% figure, Dr. Howard testified, represents "how much liquid . . . [is necessary] to achieve the level of wetness which [Mrs. Bourne] described in her deposition." (Howard Dep. at 255.)[4] He also testified, however, that he engaged in back-calculation to arrive at the 5% figure, stating that the 5% is an "estimate of the volume of Benlate mixture in a one gallon can that would need to be splashed onto Mrs. Bourne to achieve 20 percent per billion[5] of benomyl equally

---

[4] While Dr. Howard was deposed on a number of occasions, the deposition transcript representing the first 5 dates on which he was deposed appear on consecutively numbered pages. References to these first 5 dates (October 30, 1998; October 31, 1998; December 10, 1998; December 11, 1998; and April 30, 1998.) will hereinafter be referred to as "Howard Dep. at ..." Dr. Howard's most recent deposition was taken on October 4, 2001, and the transcript of the deposition begins anew with page number 1. References to the October 4, 2001, deposition transcript will be designated by date and page.

[5] He likely intended to say "parts per billion" rather than "percentage per billion," with 20 parts per billion being the minimum concentration of benomyl which several in vitro studies found to be the lowest effect level for cells dosed with benomyl. See infra III.C. Dr. Howard has adopted the EPA-utilized 3.5%

distributed throughout her body with a dermal transmission rate of 3.5 percent of the dose." (Id. at 117.)

The 5% of a gallon, which is 225 milliliters,[6] or 225,000 microliters, was spread, Dr. Howard opines, over 30% of Mrs. Bourne's body. (Id. at 331.) Mrs. Bourne's body surface area, based upon her height and weight, is found by him to be 15,000 square centimeters, with 30% thereof being 4,500 square centimeters. (Id. at 332.) Dr. Howard opines that Mrs. Bourne's dermal exposure to Benlate mixture was 50 microliters per square centimeter, or 12.5 micrograms of benomyl per square centimeter. (Id. at 332-333.)[7]

Dr. Howard admits that these figures are not measured values, but are estimates based upon Mrs. Bourne's deposition testimony. (Id. at 333-334.) Dr. Howard conducted no testing or measurements to arrive at his figures. (Id. at 255, 295, 331-34,

---

dermal absorption rate for benomyl through human skin.

[6] In his deposition, he estimated a UK gallon to be at 4500 milliliters, leading to the 225 figure. A UK gallon is actually 4546.09 milliliters, with 5% thereof being 227.3.

[7] It appears that Dr. Howard used primarily volume measures in his depositions and metric weight measurers in his report. Using metric weight, Dr. Howard concluded that the weight of 5% of the benomyl present in the UK gallon was 56.25 milligrams, with a total amount deposited per square centimeter on Mrs. Bourne's skin at 10,000 nanograms. (Howard report at 3.)

670-71.) He is unsure how much, if any, of the purported 50 microliters per square centimeter of the Benlate mixture either ran off of Mrs. Bourne's skin or was rubbed off onto her clothing. (Id. at 337-38.) He did not address a published study conducted by DuPont examining dermal exposure to Benlate in a home garden setting which concluded that dermal exposure to benomyl using two gallons of Benlate containing approximately 9.5 grams of benomyl in a compression sprayer was less than 1 milligram of benomyl. See Leighton P. Everhart & Richard F. Holt, Potential Benlate Fungicide Exposure During Mixer' Loader Operations, Crop Harvest, and Home Use, 30 J. Agric. Food Chem. 222 (1982)("DuPont Everhart study"). Converting 1 milligrams to 1,000 micrograms and dividing by 4,500, the number of square centimeters of Mrs. Bourne's body Dr. Howard contends was exposed to the Benlate mixture, then dividing by 2 to account for the study's use of 2 gallons, one is left with a figure of .11 micrograms per square centimeter. Dr. Howard's estimate of 12.5 micrograms per square centimeter exceeds this figure by about 113 times. (Howard Dep. at 333.) Nor did he address a study conducted by the National Institute for Occupational Safety and Health ("NIOSH") which found that nursery workers engaged in weighing, mixing, and applying Benlate with compression sprayers are exposed to between .14 and .19 micrograms of Benlate per

square centimeter per hour on the thigh and lower leg. Hoekstra, Kiefer, and Tepper, Monitoring of Exposure to Benomyl in Nursery Workers, 38:8 J. Occup. Environ. Med. 775,779 (1996) ("NIOSH Hoekstra study") Dr. Howard's estimate of 12.5 micrograms per square centimeter would exceed the range found in that article by 66 to 89 times. Aside from a failure to address at least the NIOSH study, Dr. Howard points to no study supporting his calculation.

B. Dermal Absorption

The estimate of the dermal transmission rate of benomyl into human blood varies based upon the source. DuPont's expert, Dr. Howard I. Maibach, opines that the human dermal absorption rate for benomyl is less than 1%, whereas the United States Environmental Protection Agency ("EPA") has adopted a 3.5% dermal transmission rate and the California EPA refers to a 10% dermal transmission rate.[8]

---

[8] Based upon the court's review of documents generated by the EPA's Hazard Identification Assessment Review Committee, on behalf of the Office of Pollution Prevention: Pesticides and Toxic Substances, the 3.5% dermal absorption rate and the referenced dermal dosage levels of benomyl appear to be utilized by the EPA merely for "the risk assessment for benomyl, and its primary metabolite carbendazim [MBC]." It does not appear that the EPA has made determinations about benomyl and its causation of teratogenic effects in humans. See Memorandum dated March 20,

The dermal absorption rates of both the EPA and the California EPA are based upon rat studies. The EPA's figure is based upon a study conducted in 1978-79 by Belasco involving the dermal absorption of benomyl on rat skin. In this study, the dermal absorption rate was 3.5% after 10 hours at a .1 milligram dose, but with lower absorption rates for lesser time intervals.[9] The study found that the dermal absorption rate decreased as the doses of benomyl applied to the skin increased. (Ex. 29-30, Def.'s Mot. Exclude.) The California EPA's dermal absorption rate appears in a 1999 document entitled Benomyl (Benlate) Risk Characterization Document. The document states that it "assumes" a 10% dermal absorption rate based upon another California EPA report prepared in 1998, entitled Estimation of Exposure to Persons in California to Pesticide Products that Contain Benomyl, by David Haskell and Louise Mehler. The 1998 report, referring

---

2001, from Deborah Smegal, Toxicologist, entitled, "Benomyl and Carbendazim-Endpoint Selection for Incidental Oral Ingestion for Carbendazim."

[9] In the Belasco study, the dermal absorption level after 4 hours was 1.7% at a .1 milligram dose, .3% at a 1 milligram dose, .04% at a 10 milligram dose, and .03% at a 100 mg dose. After 10 hours of dermal exposure, the amount absorbed was 3.5 % at a .1 milligram dose, .5% at a 1 milligram dose, and .09% at a 10 milligram dose, and .03% at a 100 milligram dose.

to the Belasco rat study, utilizes a 10% dermal absorption rate. (Ex. 27-28, Def.'s Mot. Exclude.)

Based upon his estimation that Mrs. Bourne was dermally exposed to 56.25 milligrams of Benlate with each use, Dr. Howard calculated Mrs. Bourne's total amount of benomyl absorption using several different dermal absorption rates.[10] With a 5% transmission rate, 500 nanograms per square centimeter would be absorbed; with a 3.3% transmission rate, 330 nanograms per square centimeter would be absorbed, and with a 2% transmission rate, 200 nanograms per square centimeter would be absorbed. (Howard report at 2.) Assuming Mrs. Bourne has a blood volume of 4 liters, and converting nanograms to milligrams and then dividing by one million, Dr. Howard concluded that the amount of benomyl absorbed by Mrs. Bourne was 562, 375, or 225 parts per billion, with 5%, 3.3%, and 2% dermal absorption rates, respectively. (Howard Dep. at 361-62.) DuPont contends that there is no reliable evidence underlying Dr. Howard's use of these dermal absorption figures inasmuch as they are based solely on rat studies. Indeed, DuPont points out, plaintiff's own benomyl dermal absorption study, referred to below, lends no support to

---

[10] He testified at deposition that the "rate" is in "a non-temporal context." (Howard Dep. at 119.)

Dr. Howard's contention. It appears to be the only such study of living humans.

Plaintiff nevertheless asserts that in addition to the California EPA rat dermal absorption study finding a 10% dermal absorption, a study conducted for plaintiffs by TNO ("TNO study") in the Netherlands and led by W. Mueling, involving human dermal absorption of benomyl, provides "compelling evidence" of a dermal transmission rate of at least 3.5%. (Pl.'s Resp. Motion to Exclude Howard and Tackett at 28.) Drs. Howard and Tackett address the TNO study generally in their reports to state that the study provides evidence that benomyl applied dermally becomes bioavailable.[11] In the TNO study, the skin of eight adult human volunteers was dosed with 60 milligrams of Benlate solution, containing approximately 30 milligrams of benomyl, on both upper thighs for a four hour period. The blood of the test subjects was collected via canula for 6 hours following exposure, with the urine of the subjects collected for 72 hours following exposure. (TNO study at 3, attached as exhibit 36, Def.'s Motion to Exclude.) Urine and blood samples were also taken prior to Benlate administration. (Id.)

---

[11] Bioavailability is a term used to indicate the extent to which a chemical reaches tissues or bodily fluids, such as blood plasma, and is available to be transported throughout the body.

The study was conducted in two phases. In the first phase, the samples were analyzed by high performance liquid chromatography ("HPLC") to detect and measure benomyl metabolites MBC, 5-HBC, and STB. (Mueling Dep. at 74-76.) MBC is the only benomyl metabolite that Drs. Howard and Tackett believe to be teratogenic. (Howard Dep. at 240, 401-02; Howard 10/04/01 Dep. at 97-98; Tackett Dep. at 59.) Specifically, 5-HCB is not claimed by Drs. Howard and Tackett to be teratogenic. (Id.)

No MBC or STB was detected in any blood sample and only 1 of 176 blood samples had a detectable, but non-quantifiable, level (i.e., a trace) of 5-HBC. (TNO study at 3.) 5-HBC was detected and measured in the urine samples. (Id.) In the second phase of the test, half of the blood and urine samples were re-analysed using a more sensitive detection method called liquid chromatography-tandem mass spectrometry. (Mueling Dep. at 74-76.) MBC was detected in some plasma samples but not at quantifiable levels. (Id.) Again there were detectable amounts of the benomyl metabolite 5-HBC found in the urine excreted for up to 72 hours following exposure.

However, the highest levels of MBC detection were found in blood plasma samples taken prior to benomyl administration, and

urine samples from four of the testing subjects tested positive for 5-HBC prior to any benomyl administration. (TNO study, Appendix 3) Mueling "speculate[s]" that the pre-dose benomyl metabolite detection could be the result of food ingested by the test subjects prior to the commencement of the study. (Mueling Dep. at 59-60.) Mueling testified that he only subtracted pre-exposure amounts of 5-HBC found in the urine and MBC found in plasma from the amounts of these metabolites found post-exposure when the pre-exposure amounts were deemed to be "significant." (Id. at 73-76.) On some test subjects, the amount of 5-HBC found pre-exposure was subtracted from the post-exposure amount, and on others it was not. (Id.) No amounts of pre-exposure MBC in plasma were subtracted from post-exposure MBC amounts. (Id.)

Mueling testified that no conclusions could be drawn from the second portion of the study and that other than listing those results in the TNO study report, he did not use the results for any other purpose. (Id. at 75-77.) The first portion of the study found "the plasma levels did not reach the limit of detection [and] [w]hat cannot, therefore, be determined from this investigation is the degree of skin exposure at which plasma levels of benomyl would have become detectable, which (naturally)

would occur when the clearance rate of the liver was being exceeded." (TNO study at 24.)

It is the presence of the 5-HBC metabolite in the test subjects' urine samples which Drs. Howard and Tackett contend support their 3.5% dermal absorption rates for Benlate on human skin. Dr. Howard contends that the 5-HBC evidences the amount of benomyl that had at one time been absorbed through the skin of the test subjects before being excreted in their urine. (Howard 10/04/01 Dep. 53-64.) Despite the fact that no quantifiable MBC was found in the plasma of the test subjects, Dr. Howard, using the respective molecular weights of 5-HBC and the benomyl metabolite MBC, took the measured amounts of 5-HBC present in the test subject's urine to calculate what he contends is the amount of benomyl that was absorbed through their skin to become bioavailable in the form of MBC in their blood. (Howard 10/04/01 Dep. at 61.) While his specific mathematical computations of the back-calculation of 5-HBC to MBC[12] are not made a part of the record in this case, based upon this back calculation, Dr. Howard contends that a 3.5% dermal absorption rate is "conservative." (Id. at 62-63.) Dr. Tackett adopted Dr. Howard's calculations of

[12] These computations were apparently exhibits to his October 4, 2001, deposition but were not submitted to the court.

the amount of benomyl bioavailable in the subjects of the TNO study. (Tackett Dep. at 211, 224.)

C. Teratogenicity

In addition to concluding that Mrs. Bourne was exposed to benomyl which was absorbed into her body through her skin, Drs. Howard and Tackett opine that benomyl is a human teratogen, capable of causing the plaintiff's anophthalmia. They rely upon in vivo[13] studies, involving injections of Benlate into laboratory rats and in vitro[14] studies, examining the effect of Benlate on living human cells, for their assertions that benomyl is a human teratogen. The first in vivo study relied upon by Drs. Howard and Tackett was conducted by Dr. Robert Staples in 1980 and involved benomyl administration via stomach tube to pregnant rats at doses of 3 milligrams, 10 milligrams, 30 milligrams, 62.5 milligrams, and 125 milligrams per kilogram of body weight per day. (Ex. 9, Def.'s Mot. Exclude.) In the first of two in vivo studies by Dr. Staples, both sponsored by DuPont, 2 of 251 rats at the 10

---

[13] In vivo tests are conducted on living animals.

[14] In vitro tests involve the exposure of isolated cell systems to a particular substance under controlled laboratory conditions within a test tube or petri dish.

milligram dose level bore offspring with micropthalmia.[15] At the 30 milligram level, 1 of 238 offspring had micropthalmia, and at the 62.5 milligram level, 10 of 213 offspring had micropthalmia. This study concluded that the lowest effect dose of benomyl appeared to be 10 milligrams per kilogram of weight per day. (Id.) In the second study, Dr. Staples found a lowest effect dose, or lowest observable effect level ("LOEL"), at 62.5 milligrams per kilogram of weight. A no observable effect level ("NOEL") of 30 milligrams per kilogram per day was adopted by Dr. Staples based upon the second study.

Drs. Howard and Tackett cite to another rat gavage study conducted by a professor at the University of California in 1991 which revealed ocular abnormalities in 43% of rat offspring at a dose level of 62.4 milligrams per kilogram of weight. E. Hoogenboom, Effects on the Fetal Rat Eye of Maternal Benomyl Exposure, 10 Current Eye Research 7, 601-612 (1991) (Ex. 12, Def.'s Mot. Exclude.) Another rat gavage study performed by Culick in 1981 wherein 125 milligrams per kilogram per day of benomyl were injected into pregnant rats revealed teratogenic effects. Robert Culick, Determination of Benomyl/Methyl-2-

---

[15] Micropthalmia, a condition related to anophthalmia, involves being born with underdeveloped eyes.

Benzimidazole Carbamate (MBC), 4-OH MBC and 4-OH MBC Concentration in Maternal Blood and in the Concepti of Rats Exposed to Benomyl by Gavage, Haskell Report No. 970-80. Finally, a whole body autoradiography study ("Covance study"), sponsored by DuPont, revealed a concentration of benomyl in the uveal tract, the area lining the inside of the eye behind the cornea. Whitby, C-Benomyl: Quantitative Whole Body Autoradiography Following Oral Administration (2mg/kg) to Female Pigmented Rats, Covance Laboratories (1998) (Ex. 49, Def.'s Mot. Exclude.)

In addition to using in vivo rat studies to support their contention that benomyl is a human teratogen, Drs. Howard and Tackett also used in vitro tests. Dr. Howard relies upon in vitro tests conducted by Dr. Dick Van Velzen and Dr. Graham McLean. Dr. Tackett relied only on the in vitro study of Dr. McLean. Dr. Van Velzen, in studies performed in 1996 and 1997, dosed human fetal lung cells, fibroblasts, in varying concentrations of Benlate for a period of 24 hours. He then examined the cells to ascertain the smallest amount of Benlate concentration at which there was any observable effect on the cell through micronuclei[16] formation, and in 1997, through both micronuclei formation and DNA reduction. (Van Velzen Dep. at 73.)

[16] Dr. Van Velzen described micronuclei as simply "very small nuclei." (Van Velzen Dep. at 73.)

Van Velzen inferred that cell death, or aptosis, was occurring based upon the increased formation of micronuclei and a reduction in DNA. Id. at 74. Van Velzen found a LOEL at 25 parts per billion benomyl. (Van Velzen Dep. at 298.) He found a NOEL at 20 parts per billion benomyl. (Id. at 300-303.)

Dr. McLean, in a similar in vitro study conducted in 1997, exposed human cancer nerve cells, neuroblastomas, and rat cells, to benomyl of varying concentrations for 24 hours. (McLean Dep. at 77-78.) He reported a LOEL for the rat cells at 3 parts per billion benomyl. McLean, et al., The Effect of Benomyl on Neurite Outgrowth in Mouse NB2A and Human SH-SY5Y Neuroblastoma Cells *In Vitro*, NeuroToxicology 19 (4-5):629-631 (1998).

Based upon these in vitro and in vivo tests, Drs. Howard and Tackett inferred that benomyl is a human teratogen and extrapolated the human threshold dose for teratogenicity.

D. Epidemiology

In reaching their opinions with respect to causation, Drs. Howard and Tackett considered three epidemiological studies relating to pesticide exposure and birth defects, but rejected those studies as irrelevant and unreliable, based upon the opinions of plaintiff's expert epidemiologist, Dr. David Ozonoff.

1. Spagnolo study

A 1994 study by A. Spagnolo was conducted "following the report of clusters of anophthalmia and microphthalmia in England and Wales and their possible relation to the pesticide Benomyl." See A. Spagnolo, et al., Anophthalmia and Benomyl in Italy: A Multicenter Study Based on 940,615 Newborns, Repro. Toxicology 8:397-403, 397 (1994). In this two-part study, the authors utilized registries of birth defects to identify 111 children with anophthalmia and microphthalmia born in Italy between 1986 and 1990, of a total of 940,615 births. After controlling for defects associated with chromosomal abnormalities, the authors divided Italy into regions and, in the first part or ecological portion of the study, examined the relationship between incidence of birth defects and use of benomyl by region. The results revealed a negative, nonsignificant coefficient, with there being a negative relationship between increased benomyl use by region and the incidence of anophthalmia and microphthalmia. Id. at 401.

In the second part or case control portion of the study, the authors examined the relationship between parental occupation and the incidence of children with eye defects by identifying children with anophthalmia and microphthalmia from the birth defect registries. The authors used the birth records to identify

those children with parents who worked in the agricultural field. Of the 111 children with anophthalmia and microphthalmia as just noted, information on parental occupation was available in 90 of the 111 cases. Of those 90 cases, 4 had a parent with an agricultural occupation. Id. at 401-02. After excluding the defects associated with chromosomal abnormalities, there were 63 cases of anophthalmia and microphthalmia in which parental occupation information was available. Two of the children had a parent with an agricultural occupation. Id. at 402. The second phase of the study "did not show a significant association between agricultural occupation and anophthalmia and microphthalmia at birth." Id. at 402.

Dr. Ozonoff contends that the Spagnolo study is "incapable of providing information on the risks of anophthalmia/microphthalmia to the offspring of exposed pregnant women from Benlate exposure." (Ozonoff report at 5.) He maintains that the study does not examine the relationship between prevalence of exposure and prevalence of a health outcome inasmuch as the study does not measure individual exposure to benomyl, but instead compares disease prevalence with benomyl's use by region in Italy. (Id. at 6,8.) He contends that the results are "fundamentally uninterpretable in terms of the risks of Benlate to

individuals."[17] (Id. at 9.) In his report, Dr. Ozonoff does not mention the second portion of the study examining parental occupation and its relationship to anophthalmia and microphthalmia except to state in a conclusory manner that an exposure surrogate,[18] consisting in this instance of parental occupation as an agricultural worker, for benomyl exposure is likely to be misclassified. (Id. at 12.)

In his evidentiary deposition, Dr. Ozonoff expounded on his report by stating that one who was employed as an agricultural worker in Italy during the relevant time period was not necessarily exposed to benomyl. (Ozonoff Dep. Dec. 17, 2001, Depo. at 154-56.) He testified that even assuming farm workers were exposed to benomyl, the subjects could have been all male or non-pregnant females, which would not have yielded useful results.

---

[17] Dr. Alexander M. Walker, M.D., Ph.D., DuPont's expert epidemiologist, testified that he does "not rely on the ecological portion of the Italian study for [his] opinion." (Walker Aff. at ¶ 26.)

[18] Explaining the term "exposure surrogate," Dr. Ozonoff testified, "[s]ometimes you just don't have that information, especially if it's something that occurred in the past when nobody was around to observe it or if it's too expensive to obtain that information by interviewing everybody, so you try and use some indicator of what exposure might have been; for example, an occupation, and some occupations will be much better exposure surrogates than others for particular exposures." (Ozonoff Dep. Dec. 17, 2002, at 98.)

(Id.) He also indicated that, while birth defect registries are mandatory, it is quite common that they aren't filled in, making it difficult to tell whether all the cases of a particular defect were properly recorded. (Id. at 150-51.) Upon cross-examination, Dr. Ozonoff testified that while not desirable, the use of exposure surrogates is common in epidemology. (Id. at 96-97.)

Dr. Ozonoff also testified that it would be "possible" but "extremely difficult" to design and conduct an epidemiology study to test the hypothesis of whether or not there is an association between benomyl exposure and anophthalmia. While he testified that he doesn't "know very much about ... the prevalence of Benlate exposure" in different populations, he stated that where the outcome, anophthalmia, is rare, and the exposure to benomyl is rare as well, "there is no real design you can use." (Ozonoff Dep. Dec. 17, 2001, at 129.) He refers to no studies or reports to support his opinion about the difficulty of designing such a study. Nor does he set parameters for what level of exposure and/or outcome would constitute "rare." He testified that if exposure to Benlate is not rare, then it would be possible to design a case control study examining the association between benomyl exposure and anophthalmia. (Id. at 130.)

2. Kristenson study

In a study published in 1997, the authors examined the relationship between the prevalence of birth defects as reported to the Medical Birth Registry of Norway from 1969 to 1989 out of a total of 192,417 births, and parental occupations in farming. The study found significant correlations between parental occupation in farming and several birth defects, but not eye malformations. P. Kristenson, et al., Birth Defects Among Offspring of Norwegian Farmers, Epidemiology 8:537-44 (1997). This 1997 published study does not mention benomyl but refers only to pesticides generally. However, in a letter to the editor of the British Medical Journal published in 1994, Kristenson offered an additional description of the same study and its results. The letter states in relevant part:

> Benomyl was introduced in Norway in 1971. It is mainly used as a fungicide in greenhouses and orchards; it is also used to a limited extent during the spring in fields of vegetables and, since the mid-70s, in the late autumn in the grain fields. Its use has been limited in Norway: the maximum sale was 1682 kg active compound in 1980. We considered farm activities after 1970 that might result in exposure of benomyl at a relevant time: work in greenhouses throughout the year; in orchards for children conceived in April-June; with vegetables grown in fields for children conceived in August-November. Eleven percent (n=21843) of the entire cohort of infants born in 1967-91 had potentially been exposed to

> benomyl according to these criteria. Four of the 192416 [sic] children had been diagnosed as having anophthalmia or microphthalmia.... Our data do not indicate that parental agricultural activity is a specific risk for anophthalmia in children. Even with this large cohort, comprising roughly a seventh of all births in Norway during the period studied, no firm conclusions concerning this rare birth defect can be drawn. The use of proxies as exposure variables adds to the uncertainty. Nevertheless, our data do not support the suggestion that benomyl is a risk factor.

Kristenson, P. "Clusters of anophthalmia: No link with benomyl in Italy ... or in Norway." BMJ, 308: 206-207, 1994.

Dr. Ozonoff disregards the Kristenson study because the 1997 published study does not mention benomyl but refers only to pesticides generally. With respect to the letter to the editor by Kristenson which appears to further describe the results of his study as it related to benomyl, Dr. Ozonoff maintained simply that the study "is not informative as to the question of whether [bemomyl is] a risk factor." (Ozonoff Dep. Dec. 17, 2001, at 85.) In his report he also noted that the study might have erroneous results as a consequence of the failure to recognize less conspicuous forms of microphthalmia or cases in which microphthalmia is a concomitant malformation, and because the use of Benlate in Norway was very restricted during the relevant time.

(Ozonoff Rep. at 11.) Neither his report nor his evidentiary deposition explain the basis for his statement that the use of Benlate in Norway was then very restricted.

3. Dolk study

A study examining geographical variation in anophthalmia and microphthalmia in England published in 1998 investigated the allegations of an English newspaper that there were "clusters" of blind children in England in farming areas associated with Benlate use. H. Dolk, et al., Geographical Variation in Anophthalmia and Microphthalmia in England, 1988-1994, British Medical Journal, 317:905-09. The study found that the overall prevalence of anophthalmia and microphthalmia in England was 1 in 10,000 births and found no statistically significant variation from region to region of England. Id. at 907.

Dr. Ozonoff does not discuss the Dolk study in his report except to state that "the existing data from England and Norway is similarly without relevance to this question [the risk of anophthalmia and microphthalmia to the offspring of exposed pregnant women to Benlate]."[19]

[19] Dr. Ozonoff testified at his discovery deposition taken October 23, 1998, that at the time he drafted his report, he had not read the Dolk study, which had not yet been published.

Dr. Howard and Dr. Tackett both relied upon Dr. Ozonoff's opinions regarding the irrelevance of the epidemiological studies relating to Benlate use and anophthalmia and microphthalmia. (Howard report at 1.) Inasmuch, however, as Dr. Ozonoff acknowledged that the use of exposure surrogates, as in the Spagnolo study, is common in the field of epidemiology, and considering he provided only conclusory and speculative remarks about the Kristenson study and the Dolk study, it appears that the blanket rejection by Drs. Howard and Tackett of these epidemiological studies was unfounded. The court finds this particularly to be true when plaintiff had pointed to no epidemiological evidence supportive of his position.

III.

DuPont seeks to exclude the testimony of Drs. Howard and Tackett on several grounds. DuPont asserts that (1) Drs. Howard and Tackett are not qualified to render the opinions they offer; (2) they failed to perform a differential diagnosis of the plaintiff; (3) the methodologies of Drs. Howard and Tackett of relying upon single-species high dose animal studies and in vitro

---

(Ozonoff Dep. October 23, 1998, at 19.) He testified that reading the study did not alter his opinion. (Id. at 19-20)

cell culture tests, without relying upon relevant epidemiological data, to draw conclusions about human teratogenesis via dermal absorption, is not scientifically valid, reliable, or generally accepted pursuant to Federal Rules of Evidence 104, 402, and 702; (4) Dr. Howard's calculations of the dose of Benlate to which Mrs. Bourne was exposed, and Dr. Tackett's ratifications thereof, are imprecise and invalid; (5) the dermal absorption rates utilized by Drs. Howard and Tackett were derived using unreliable and scientifically invalid bases; and (6) Drs. Howard and Tackett misuse EPA and EU regulatory processes and recommendations as if they were causation determinations.

In response, plaintiff asserts that, while each piece of data underlying the conclusions of Drs. Howard and Tackett may not be sufficient to independently justify the experts' conclusions, taken as a whole the body of data relied upon by Drs. Howard and Tackett support their conclusions, rendering their methodologies sound.

IV.

Effective December 1, 2000, Federal Rule of Evidence 702 was amended to reflect the United States Supreme Court's landmark

decision of Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993). The revised Rule 702 states:

> Testimony by Experts -- If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702. As the Advisory Committee Notes indicate, the amendment to Rule 702 is consistent with the district court's "gatekeeping" function as articulated in Daubert. The proponent of the proposed expert testimony must establish its admissibility by a preponderance of proof. See Daubert, 509 U.S. at 592 n.10; Fed. R. Evid. 104(a).

In Daubert, the United States Supreme Court charged trial judges with the responsibility to act as "gatekeepers" to "ensure that any and all scientific testimony . . . is not only relevant, but reliable." Daubert, 509 U.S. at 589. As a part of its analysis, a trial court is to determine "whether the expert is proposing to testify to (1) scientific knowledge that (2) will

assist the trier of fact to understand or determine a fact in issue." Id. at 592. It is for the trial court to make the "preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." Id. at 592-93. As to the first prong of the inquiry, whether the expert offers "scientific knowledge," the analysis focuses on whether the subject of the expert's testimony is grounded in the "methods and procedures of science," and constitutes "more than subjective belief or unsupported speculation." Id. at 590. In order to qualify as "scientific knowledge," an inference or assertion must be derived by the "scientific method." Id. That is, the testimony must be supported by "'good grounds,' based on what is known." Id.

The Supreme Court in Daubert set forth a flexible, non-exhaustive checklist of four factors for trial courts to utilize in their evaluations of reliability. Id. at 593-94. These factors include: (1) whether a theory or technique can be or has been tested; (2) whether it has been subjected to peer review and publication; (3) whether a technique has a high known or potential rate of error and whether there are standards controlling its operation; and (4) whether the theory or technique enjoys general

acceptance within a relevant scientific community. Id. at 592-94. In a later opinion, the Court further emphasized that these factors are flexible, not rigid, may or may not be pertinent in a given case and are to be applied based upon "the particular circumstances of the particular case at issue." Kumho Tire Co. v. Carmichael, 526 U.S. 137, 150 (1999).

The second prong of the Daubert analysis focuses on whether the expert's testimony will be helpful to the trier of fact in deciding a fact in issue. Included in that analysis is the question of relevancy or "fit." Id. at 591. The expert's proffered scientific testimony must be sufficiently tied to the facts of the case that it will be of assistance to the factfinder in resolving a disputed fact. Id. (citing United States v. Downing, 753 F.2d. 1224, 1242 (3rd Cir. 1985)). That is, there must be a "valid scientific connection to the pertinent inquiry" before the testimony is admissible. Id. at 591-92.

The Court noted in Daubert that "vigorous cross examination, presentation of contrary evidence and careful instruction on the burden of proof are traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 596. However, when making the determination as to

admissibility, a trial judge has considerable leeway in both the determination of reliability and the means the judge uses to make it. See Kumho Tire Co., 526 U.S. at 152.

V.

The court does not propose to question the qualifications of Drs. Howard and Tackett for purposes of this order.[20] The court must determine, pursuant to Daubert, first, whether the proffered testimony constitutes "scientific knowledge," grounded in the "methods and procedures of science," and is "more than subjective belief or unsupported speculation," and second, whether the proffered testimony "fits" with the factual inquiry of the case. See Daubert, 509 U.S. at 589-91.

A. General Causation

Drs. Howard and Tackett have derived their general causation theory, that benomyl is teratogenic to humans, based

---

[20] In a rather factually similar civil action, E.I. DuPont De Nemours & Co., Inc. v. Castillo, 748 So.2d 1108 (Fla. 3d DCA), review granted, (Fla. 2000) ("Castillo"), wherein plaintiff alleged that his mother's dermal exposure to Benlate caused his anophthalmia, the intermediate appellate court of Florida excluded the testimony of Dr. Howard but found nonetheless that he was qualified under the Florida Rules of Evidence to render his proffered opinions. The Florida Supreme Court granted certiorari and oral arguments were presented on February 6, 2001.

solely upon in vivo rat gavage studies and in vitro tests. They discredit the only existing human data, consisting of epidemiological studies reflecting no statistical relationship between potential Benlate exposure and human birth defects. They also disavow gavage benomyl testing on different animal species -- the mouse and the rabbit -- which have revealed no ocular abnormalities in the offspring.

There can be no dispute that properly designed and conducted animal testing can yield relevant and useful information in the field of human toxicology. See, e.g., Turpin v. Merrell Dow Pharmaceuticals, Inc., 959 F.2d 1349, 1360-61 (6th Cir. 1992), cert. denied, 506 U.S. 826 (1992) ("We do not mean to intimate that animal studies lack scientific merit or power when it comes to predicting outcomes in humans. Animal studies often comprise the backbone of evidence indicating biological hazards, and their legal value has been recognized by federal courts and agencies. Here, the record's explanation of the animal studies is simply inadequate. . . . The record fails to make clear why the varying doses of Bendectin or doxyalamine succinate given to the rats, rabbits and in vitro animal cells would permit a jury to conclude that Bendectin more probably than not causes limb defects in children born to mothers who ingested the drug at prescribed doses

during pregnancy."). Likewise, in vitro tests provide useful information about metabolic processes at a cellular level, and may supplement existing animal and human data. See, e.g., Allen v. Pennsylvania Engineering, 102 F.3d 194, 198 (5th Cir. 1997) (in vitro data shows only that ethylene oxide has mutagenic and genotoxic capabilities in living organisms, not that it necessarily causes brain cancer in humans). However, the extrapolations of Drs. Howard and Tackett, from high-dosage, single species in vivo testing and lengthy benomyl exposure in vitro testing, to conclude that benomyl is a human teratogen and to establish the levels at which it is alleged to be teratogenic, are neither reliable, pursuant to the first prong of Daubert, nor relevant, under the second prong.

Courts considering the reliability of experts' extrapolation to human teratogenicity from in vivo and in vitro tests have recognized that such tests are generally considered to be suspect when relied upon for that purpose. In the absence of other strong indicators of the reliability of in vivo and in vitro tests, including supporting epidemiological studies, testing on closely related species,[21] and the use of comparable dosages,

[21] Primates are considered to render the most persuasive results with respect to extrapolation of the results to humans, followed by other mammals, then birds, followed by reptiles. See

courts have overwhelmingly found unreliable the methodology of extrapolating human teratogenicity from in vivo and in vitro tests. See, e.g., Raynor v. Merrell Pharms., Inc., 104 F.3d 1371, 1374 (D.C. Cir. 1997) (concluding it was not methodologically sound for experts to draw inference from chemical structure studies, in vivo animal studies, and in vitro studies, that Bendectin caused human birth defects, when epidemiological evidence was to the contrary); Allen, 102 F.3d at 198 (excluding expert testimony as unreliable where in vivo tests were inconclusive and in vitro tests could not be extrapolated to establish human teratogenicity); Conde v. Velsicol Chem. Corp., 24 F.3d 809, 813 (6th Cir. 1994) (finding experts were unable to connect chemical chlordane with plaintiffs' injuries using in vivo and in vitro tests, in light of plaintiffs' low level of exposure to the substance and contradictory epidemiological evidence); Sorensen v. Shaklee Corp., 31 F.3d 638, 646 n.12 (8th Cir. 1994) ("Because of the dose-response differential between animals and humans, however, extrapolating to humans from animal studies is problematic."); Turpin, 959 F.2d at 1360-61 ("The record fails to

---

Erica Beecher-Monas, The Heuristics of Intellectual Due Process: A Primer for Triers of Science, 75 N.Y.U. L. Rev. 1563, 1608 (2000) (citing Larry C. Gilstrap & Bertis B. Little eds, Drugs and Pregnancy 9 (2d ed. 1998) (noting that "nonhuman primates are better predictors...than are nonprimate models because they are phylogenetically close to humans")).

make clear why the varying doses of Bendectin or doxyalamine succinate given to the rats, rabbits and in vitro animal cells would permit a jury to conclude that Bendectin more probably than not causes limb defects in children born to mothers who ingested the drug at prescribed doses during pregnancy."); [22] Richardson v. Richardson-Merrell, Inc., 857 F.2d 823, 830 (D.C. Cir. 1988), cert. denied, 493 U.S. 882 (1989) (finding that chemical structure activity analysis and in vitro and in vivo studies used by plaintiff's expert cannot furnish sufficient foundation for

---

[22] The court in Turpin, referring to an authoritative text on teratology, explained why animal testing cannot be directly extrapolated to human beings:

> "A recognized text on teratology states the customary scientific view that 'it has become axiomatic in experimental teratology that agents capable of causing any adverse biological effects can usually also be shown to be embryotoxic under the right conditions of dosage, developmental stage, and species susceptibility,' and that 'virtually all drugs and a great range of chemicals can indeed be shown to be embryotoxic under appropriate laboratory conditions. . . . The author concludes that to 'eliminate drugs and chemicals because they can be shown to be embryotoxic at high dosage would be unacceptable' because to do so 'would eliminate most drugs and many useful chemicals upon which modern society depends heavily.'")

Turpin, 959 F.2d at 1359(quoting James Wilson, Current Status of Teratology, in Handbook of Teratology 60 (J. Wilson & C. Fraser, eds. 1977)).

causation opinion in the face of considerable contrary epidemiological evidence); Lynch v. Merrell-Nat'l Labs., 830 F.2d 1190, 1194 (1st Cir. 1987) (in vivo and in vitro animal tests and the tests on "analogous" chemicals, whether "singly or in combination, do not have the capability of proving causation in human beings in the absence of any confirmatory epidemiological data"); Wade-Greaux v. Whitehall Laboratories, Inc., 874 F. Supp. 1441, 1484 (D. Vi 1994), aff'd., 46 F.3d 1120 (3rd Cir. 1994) (excluding causation experts' opinion, finding high dose animal testing and in vitro animal test data are not relied upon by experts in the field of teratology for extrapolating the results found directly to the human experience); In re Agent Orange Product Liab. Litig., 611 F. Supp. 1223, 1241 (E.D. N.Y. 1985), aff'd, 818 F.2d 187 (2d Cir. 1987), cert denied, 487 U.S. 1234 (1988) ("[L]aboratory animal studies . . . are generally viewed with more suspicion than epidemiological studies, because they require making the assumption that chemicals behave similarly in different species.").

The only existing epidemiological evidence[23] is contrary to plaintiff's position. Further, in vivo benomyl testing has revealed ocular abnormalities in only a single species of animal, whereas gavage testing on both the rabbit and the mouse revealed no ocular abnormalities.[24] The court concludes that Drs. Howard and Tackett have failed to offer sufficient support for the otherwise suspect single-species in vivo tests and in vitro tests

---

[23] Drs. Howard and Tackett rely upon the opinion of Dr. Ozonoff, a physician and environmental epidemiologist, discrediting the validity of the epidemiological evidence relating to benomyl. Even assuming this methodology -- reliance upon the opinion of an expert in the field of epidemiology -- is sound, the plaintiff has no epidemiological evidence supporting the proposition that benomyl is a human teratogen. He is left, therefore, with only rat gavage tests and in vitro tests to extrapolate both human teratogenicity of benomyl and the levels of the substance capable of causing birth defects. See supra II.D.

[24] See R. Kavlock, et al., Teratogenic Effects of Benomyl in the Wistar Rat and CD-1 Mouse, with Emphasis on the Route of Administration, Toxicol. Appl. Pharmacol., 62: 44-54 (1982) (Ex. 11, Def.'s Mot. Exclude); W. Busey, Segment II - Teratology Study in Rabbits, Hazleton Leboratoris, Inc. (Unpublished Report No. MRO 1079) (1968) (Ex. 13, Def.'s Mot. Exclude); S. Munley, Developmental Toxicology Study of DPX-T1991-529 (Benomyl) in Rabbits, Newark, Delaware, E.I. DuPont de Nemours and Co., Inc., Haskall Laboratory (Unpublished Report No. HLR 164-95)(1995) (Ex. 14, Def.'s Mot. Exclude).

Dr. Tackett acknowledged at deposition that one species of animals will generally have a different teratogenic response to a chemical than will another animal species. (Tackett Dep. at 224.) Dr. Howard testified, "[i]t's usually said that to define something as a human teratogen it's desirable to have two animal models." (Howard Dep. at 672.)

to render methodologiocally sound an extrapolation of human teratogenicity.

Moreover, the rat gavage studies and the in vitro tests relied upon by Drs. Howard and Tackett, using injections of high-levels of benomyl directly into the stomach of rats and high-level in vitro dosing of cells of both rats and humans in benomyl for 24 hours, do not "fit" with the facts of the case as alleged. General Elec. Co. v. Joiner, 522 U.S. 136 (1996), is germane. In Joiner, a city electrician who suffered from lung cancer filed suit against the manufacturer of polychlorinated biphenyls (PCBs) and manufacturers of electrical transformers and dielectric fluid, alleging strict liability, negligence, fraud, and battery. The district court excluded the testimony of electrician experts and granted defendants' motion for summary judgment. The United States Court of Appeals for the Eleventh Circuit reversed. The Supreme Court considered the fact that the plaintiff's proffered causation expert relied upon studies indicating that infant mice developed cancer of a different type than the plaintiff, after receiving massive gavage doses of PCBs. Id. at 144. The Court noted that the experts never explained "how and why [they] could have extrapolated their opinions from animal studies "far removed" from the circumstances of the plaintiff's exposure to PCBs." Id.

Finding the studies upon which the experts relied to be "not sufficient, whether individually or in combination, to support their conclusions," the Court found that the district court had not abused its discretion in excluding their testimony. Id. at 146.

Similarly, the rat gavage testing relied upon by Drs. Howard and Tackett is "far removed" from the plaintiff's alleged exposure, with high doses of benomyl injected directly into the rats' stomachs. Using the Staples studies as an example, the lowest level of benomyl injection at which an ocular effect on offspring was noted was at 10 milligrams per kilogram of weight per day. A comparable dosage for Mrs. Bourne, who weighs approximately 50 kilograms, would be a direct injection (setting aside the fact that the chemical is alleged to have been absorbed dermally at a rate of 3.5%) of 500 milligrams, or one-half of one gram. Each sachet of Benlate contained approximately 1.19 grams of benomyl (based on 53% of the 2.25 gram Benlate sachet). Thus, to be comparable to the lowest observable effect level, approximately one-half of the contents of a sachet would have to be injected into Mrs. Bourne. The other rat studies relied upon by Drs. Howard and Tackett involved far greater injections of

benomyl.[25] Indeed, none of the rat studies producing teratogenic effects involved exposure to benomyl dermally or orally. With respect to the in vitro tests wherein cells were continually soaked in benomyl for 24 hours, plaintiff has made no contention that Mrs. Bourne was continually and directly exposed to benomyl for such an extended period. In sum, the analytical gap between the rat evidence relied upon by Drs. Howard and Tackett and the inferences drawn therefrom is simply too wide, rendering the extrapolations a poor "fit" for the facts of the case.

The court concludes that the methodologies of Drs. Howard and Tackett in concluding that benomyl is a human teratogen are unsound.

B. Specific causation

Even assuming, arguendo, that the extrapolations from in vivo rat studies and in vitro studies to human teratogenicity levels were scientifically sound, the court nonetheless concludes that the opinions of Drs. Howard and Tackett relating to specific causation are not scientifically valid and reliable.

---

[25] Staples second rat study produced a LOEL at 62.5 milligrams per kilogram; the Culick study injected 125 milligrams per kilogran; the Hoogenboom study used 62.4 millograms per kilogram of weight. See supra p. 15-17.

It appears that the conclusion of Dr. Howard, as adopted by Dr. Tackett, with respect to Mrs. Bourne's level of dermal exposure to Benlate, is highly speculative, without the indicia of reliability required by Rule 702 and Daubert. Rather than conducting any type of test or study to attempt to recreate the actions described by Mrs. Bourne in her deposition with respect to treating her plants with Benlate, it appears that Dr. Howard has developed arbitrary figures to represent what he deems to be the percentage of Mrs. Bourne's body exposed to Benlate and the amount of the Benlate mixture applied to her skin which he calculates to be 5% of the one-gallon Benlate mixture used periodically by her. While he contends on the one hand that the figure is based upon the portion of a gallon estimated by him as necessary to produce the level of wetness described by Mrs. Bourne, he also testified that he back-calculated the amount of dermal benomyl exposure necessary, using a 3.5% dermal absorption rate, to achieve a benomyl concentration of 20 parts per billion. (Howard Dep. at 117.) Thus, Dr. Howard's 5% figure is, at best, purely speculative and at worst, devised to ensure that a certain desired end -- 20 parts per billion -- was met. In either case, the adopted methodology, or lack thereof, is contrary to principles of sound scientific method. See, e.g., General Elec. Co. v. Joiner,

522 U.S. 136, 146 (1997) ("nothing in either Daubert or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the ipse dixit [an assertion made but not proved] of the expert"); Oglesby v. General Motors Corp., 190 F.3d 244, 250 (4th Cir. 1999) ("A reliable expert opinion must be based on scientific, technical, or other specialized knowledge and not on belief or speculation, and inferences must be derived using scientific or other valid methods.").

Additionally, the 5% figure does not take into account pertinent published studies (DuPont Everhart study and NIOSH Hoekstra study, supra p. 8-9) examining the exposure of garden users to Benlate. See, e.g., Cooper v. Smith & Nephew, Inc., 259 F.3d 194, 203-04 (4th Cir. 2002) (affirming trial court's exclusion of plaintiff's causation expert, in part, on basis that expert rejected, without offering sound explanation, medical literature and plaintiff's own medical records which tended to support another cause of plaintiff's condition). Nor is the 5% calculation capable of being tested or reproduced. Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 592-94 (1993)(setting forth non-exhaustive list of factors pertinent to whether an opinion is reliable); United States v. Dorsey, 45 F.3d 809, 814-815 (4th Cir. 1995) (affirming exclusion of expert

testimony as scientifically invalid because the methodology upon which it was based was not generally accepted, had never been peer-reviewed, and its potential rate of error was high). In sum, Dr. Howard's methodology in arriving at the 5% figure, is unreliable.

The methodology utilized by Drs. Howard and Tackett in deriving a level of human dermal absorption for benomyl likewise appears to be unsound. In his report, Dr. Howard utilized several dermal absorption rates, the lowest thereof being 2%. He identifies several sources for the dermal absorption rates, including the EPA's use of a 3.5% rate and the amount of Benlate "potentially absorbed" by the test subjects in the TNO studies. The EPA's use of a 3.5% figure is based upon a 1979 study on the dermal absorption of Benlate on rat skin wherein 3.5% was absorbed after a period of 10 hours. See supra p.9. Setting aside the fact that it is not alleged that Mrs. Bourne was exposed to Benlate for a 10 hour period, it is well established among the scientific community that rat skin is more permeable than human skin. (See Maibach Aff. at ¶ 48; Tackett Dep. at 126-27.) Dr. Tackett testified in his deposition that he believes that rabbit skin and rat skin are approximately 10 times more permeable than human skin with respect to Benlate or benomyl. While his report does not identify a specific rate which he has adopted, it

mentions the EPA's 3.5% dermal absorption rate, based on rat studies, and formulated for risk assessment, not causation, purposes. (Tackett Report at 4.) The only study relied upon by Drs. Howard and Tackett relating to the dermal absorption of benomyl on living human skin is the TNO study conducted by Mueling.[26] (See Mueling, TNO Lab Reports V3596 and V2662.) Mueling testified at deposition that based on the TNO study he was not able to determine a rate of benomyl transmission through the human skin, nor was he able to ascertain whether the rate of percutaneous absorption of benomyl is dependent upon the amount of skin which is exposed. (Mueling Dep. at 77.) The TNO study found no measurable amounts of benomyl metabolites in the blood plasma of the test subjects. (See W. Mueling, TNO Lab Reports supra 38.)

Despite the seeming lack of useful results produced by the TNO study,[27] Drs. Howard and Tackett rely upon the detectable

---

[26] A study conducted on human cadavers revealed a dermal absorption rate for benomyl of less than 1%. (ICI Central Toxicology Laboratory, Report CTL/P/3659.)

[27] Meuling testified that the TNO study failed to determine the following: the rate of transmission of benomyl through human skin; the levels achieved of the major metabolites of benomyl in blood plasma; the time it takes for benomyl metabolites to reach a peak concentration in blood plasma or how long that peak concentration persists; the speed or time at which the level of benomyl metabolites begin to drop off; the half-life of benomyl metabolites in blood plasma; whether the rate of percutaneous absorption of benomyl is dependent on or changes with the amount of skin exposed; whether the rate of percutaneous absorption of benomyl was dependent on or changed with the amount

amounts of 5-HBC in the test subjects' urine to calculate what they contend to be the dermal bioavailability of benomyl. They back-calculate the cumulative amount of benomyl and its metabolite MBC that passed through the blood and tissue of the human test subjects in the TNO study by converting the total amount of 5-HBC found in the urine of the test subjects, assuming benomyl is approximately 138% of the molecular weight of 5-HBC. (Howard Dep. at 83-85.) As DuPont's expert pharmacologist and toxicologist Michael Owens, PhD, points out, this methodology is based on the "unsupported assumption that all of the 5-HBC in the urine was at one point benomyl/MBC in the blood plasma or tissue." (Owens Aff. at ¶ 7a.) It ignores the possibility that benomyl/MBC was metabolically converted to 5-HBC in the skin, prior to reaching the blood. (Id.) The skin's conversion of benomyl to 5-HBC, is, according to Dr. Owens, the "most likely" scenario, supported by the lack of any measurable amount of benomyl or MBC found in the blood of the TNO test subjects. (Id.) Further, the back-calculation fails to account for the amounts of 5-HBC which were detected in the urine, or for that matter the MBC detected in the plasma, of the test subjects prior to administration of Benlate. See supra II.B.

---

of substance (dose) applied to a given area; and any kinetic parameters for benomyl in humans. (See Meuling Dep. at 76-78.)

It appears that the back-calculation of 5-HBC to benomyl is internally inconsistent with the very TNO study upon which Drs. Howard and Tackett purport to rely. The conductor of the study, Mueling, testified at deposition that one cannot ascertain the amount of MBC or 5-HBC in the blood based on the TNO urine data. (Mueling Dep. at 107-08.) Mueling also testified that his TNO study did not reveal a rate of transmission through human skin. (Id. at 76-78.) The court concludes that the calculations of Dr. Howard, adopted by Dr. Tackett, purporting to reflect the rate of human dermal absorption of benomyl into the blood based upon the amount of 5-HBC found in the urine of the TNO test subjects constitutes merely the "ipse dixit" of Drs. Howard and Tackett and is not grounded in "the methods or procedure of science." See General Elec. v. Joiner, 522 U.S. at 146.

Whether derived from the molecular weight of irrelevant 5-HBC metabolites in TNO test subjects' urine or extrapolated directly from the 20-year old Belasco tests involving the administration of benomyl to permeable rat skin for extended durations, the 3.5% dermal absorption rate used by Drs. Howard and Tackett cannot be said to be methodologically sound.

VI.

It appearing that the opinions proffered by Drs. Howard and Tackett meet neither the requisite standards of reliability or relevance under Federal Rule of Evidence 702, as set forth by the United States Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993) and its progeny, the court concludes that their testimony must be excluded.

Wherefore, for the foregoing reasons, it is ORDERED that DuPont's motion to exclude the testimony of Dr. Howard and Dr. Tackett be, and it hereby is, granted.

The Clerk is directed to forward copies of this order to all counsel of record and to post this published opinion at http://www.wvds.uscourts.gov.

DATED: March 29, 2002

JOHN T. COPENHAVER, JR.
United States District Judge

Plaintiff:

James L. Ferraro
Lynn M. Holtzman
Markenzy Lapointe
Diana L. Rolfs
Ferraro & Associates, P.A.
First Union Financial Center
Suite 3800
200 South Biscayne Boulevard
Miami, FL 33133

Scott S. Segal
The Segal Law Firm
810 Kanawha Boulevard East
Charleston, WV 25301

Defendant:

Patrick W. Lee
William L. Anderson
Emma K. Burton
Crowell & Moring, LLP
1001 Pennsylvania Avenue, NW
Washington, DC 20004

David B. Thomas
Philip J. Combs
Allen, Huthrie & McHugh
1300 Bank One Center
P.O. Box 3394
Charleston, WV 25333